Towards personalized cardiovascular risk management in renal transplant recipients

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Chapter 1

INTRODUCTION AND AIMS OF THESIS

INTRODUCTION

Kidney transplantation

Since the first successful operation in man in 1954, kidney transplantation has evolved from an experimental therapy to the treatment of choice for most patients with end-stage renal disease (ESRD). Kidney transplantation offers a significant survival benefit to patients with ESRD and improves their quality of life as compared with patients who remain dependent on dialysis.[1,2] As an example, the expected unadjusted remaining lifetime for a 40 year old patient on dialysis is 12.0 years, whereas this is 26.2 years for a renal transplant recipient (RTR) of the same age (Figure 1).[3] The number of kidney transplantations performed each year in the Netherlands has continued to grow over the past decades and increased from 587 in 2002 to 984 in 2015.[4] In line with this, the total number of patients in the Netherlands who now live with a functioning kidney transplant is around 16,000 and increasing.[4,5]

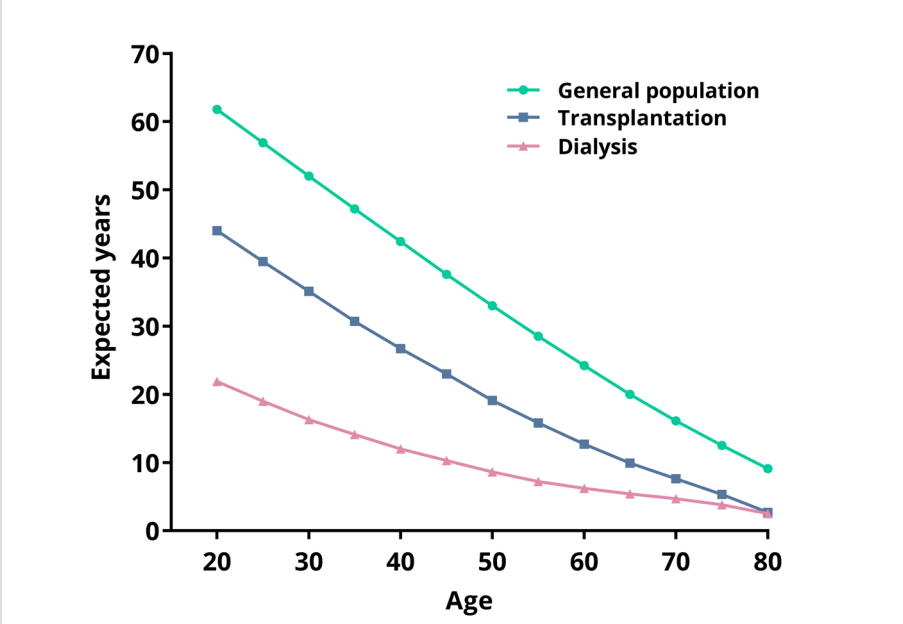

Figure 1. Expected remaining lifetime for the general population (green dots), renal transplant recipients (blue squares), and dialysis patients (pink triangles). Data from the ERA-EDTA Annual Report 2014.[3]

Long-term survival after kidney transplantation

One year graft survival after kidney transplantation has steadily improved from approximately 40% in the 1970s to more than 90% to date.[6] This is mainly the result of improved surgical techniques and advancements in immunosuppressive therapy. However, despite these improvements in short-term outcomes, there has been surprisingly little improvement in long-term outcomes over the past decades.[7,8] Moreover, observed improvements in long-term survival are mostly attributable to improvements in survival in the first months after transplantation as is depicted in Figure 2, where lines for graft survival for the different year cohorts run almost parallel beyond 6 months after transplantation. Currently, in the Netherlands, the 5-year allograft survival rate for living donor transplants is 84%, and for deceased donor transplants this is only 70%.[5] In the US, for example, these survival rates are even slightly worse.[2] The causes of long-term kidney allograft loss are multifactorial. In about half of successfully operated patients, the kidney transplant fails due to diverse causes, including recurrent primary kidney disease, and calcineurin inhibitor toxicity. The other half of allograft losses occurs because the recipient dies with a functioning kidney transplant.[9,10]

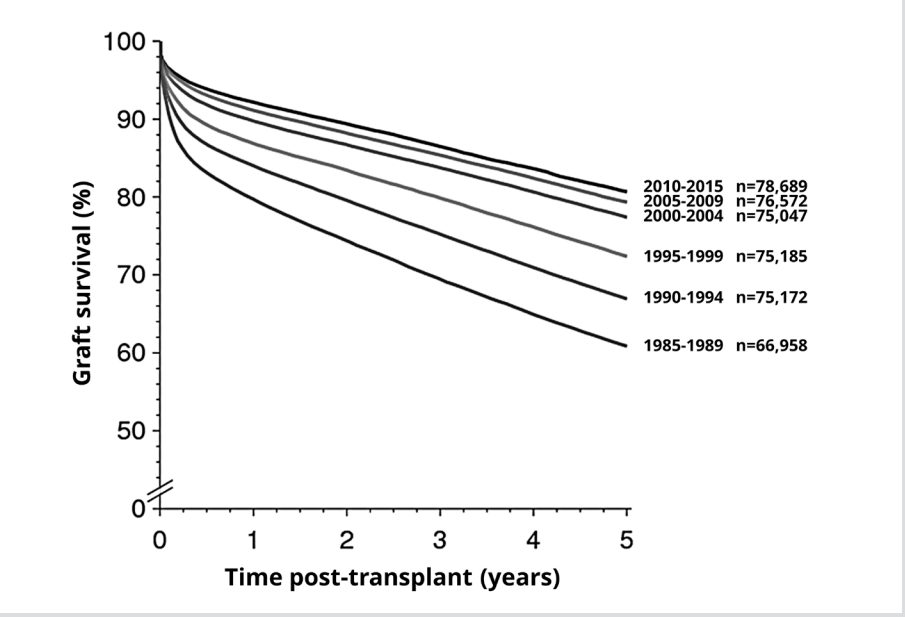

Figure 2. Allograft survival of first kidney transplants according to different years of transplantation. Data from the Collaborative Transplant Study; figure is available online at: http://www.ctstransplant.org (Figure: K-14001-0217).

Cardiovascular disease after kidney transplantation

Cardiovascular disease (CVD) is the primary cause of death of RTR, preceding infection and malignancy. Beyond one year after transplantation, age- and sex-adjusted death rates in RTR are several times higher than in the general population, primarily due to an excess in CVD.[11,12] The most common causes of cardiovascular death are myocardial infarction, left ventricular hypertrophy, sudden cardiac arrest, and stroke.[12-14] Interestingly, the cardiovascular risk profile of RTR differs from that of the general population or patients with chronic kidney disease (CKD). Many RTR already have several traditional cardiovascular risk factors before transplantation, which likely contributed to the development and progression of their underlying kidney disease in the first place (Table 1). Unfortunately, these risk factors are only partially remitted following successful transplantation. In fact, the prevalence of these traditional risk factors, such as for instance hypertension, is generally higher than in the general population or other high risk populations such as diabetes or CKD,[11,15,16] and the underlying mechanisms, as well as response to treatment may be different. Moreover, after transplantation new transplantation-related risk factors emerge, such as remaining subnormal kidney function, viral infections, and the use of immunosuppressive drugs (i.e. corticosteroids and calcineurin inhibitors) (Table 1 and Figure 3).[12-14] The risk of adverse effects of treatment with these drugs is considerable, because of the narrow therapeutic window between efficacy and toxicity. For this reason, calcineurin inhibitors are titrated by close monitoring of drug levels, but for corticosteroids, currently, no such monitoring is available, and accordingly treatment with these drugs is more or less 'one-size-fits-all'.[17] The consequences of the differences in risk profile between RTR and other populations have not been systematically investigated, and hence, cardiovascular risk management in this population is still largely based on studies in other populations, for example patients with hypertension, diabetes or CKD.[16] This might well be an underlying factor in the high CV morbidity and mortality in this population. Therefore, in order to improve long-term outcome after kidney transplantation, we are in need of comprehensive strategies to reduce increased cardiovascular risk, ideally addressing both traditional and transplantation-related risk factors, and to provide adequate transplantation-specific guidelines for cardiovascular risk management in RTR. In addition, better personalization of risk management could greatly benefit from tools (such as biomarkers) that can guide better personalization of treatment in RTR.

Table 1. Cardiovascular (CV) risk factors in renal transplant recipients.

Non-modifiable risk factors

age
sex (male > female)
ethnicity
family history
prior CV history

Potentially modifiable risk factors

Traditional risk factors	**Traditional risk factors in the transplantation setting**	**Transplantation-related risk factors**
obesity	post-transplant weight gain → obesity ↑	time on dialysis
insulin resistance / diabetes	insulin resistance / diabetes ↑	delayed graft function
hypertension	hypertension ↑	acute rejection episodes
dyslipidemia	sodium sensitivity ↑	reduced kidney function
anemia	physical inactivity ↑	proteinuria
smoking	chronic inflammation / immune activation ↑	new-onset diabetes
high alcohol intake		viral infections (e.g. CMV)
high sodium intake		corticosteroid use
physical inactivity		calcineurin inhibitor use
chronic inflammation		

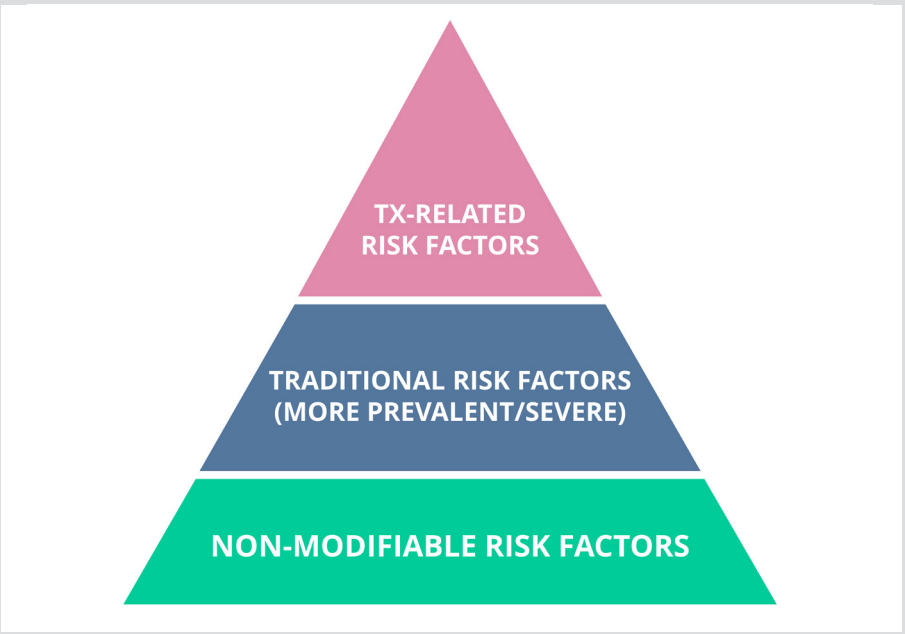

Figure 3. Accumulation of traditional and transplantation(tx)-related cardiovascular risk factors in renal transplant recipients, adding to increased cardiovascular risk.

Hypertension after kidney transplantation – The pressure is on

Of all traditional and transplantation-related cardiovascular risk factors, hypertension is the most prevalent. Up to 90% of RTR have high blood pressure or are treated with antihypertensive drugs.[12,18] There are many factors contributing to hypertension after kidney transplantation, among which are general risk factors such as an unfavorable metabolic profile (i.e. weight excess, dyslipidemia, and insulin resistance), male sex, and age, but also transplantation-related risk factors such as increased sympathetic nerve activity or vascular calcification, reduced kidney function, and treatment with calcineurin inhibitors and/or corticosteroids.[19,20] Treatment of hypertension after kidney transplantation mostly involves pharmacological treatment with a combination of different antihypertensive drugs, which are chosen based on co-morbidity, efficacy, and interactions with other drugs.[20,21] Mostly calcium channel blockers, beta- and alpha-blockers, and diuretics are prescribed.[21] Treatment with renin-angiotensin-aldosterone system (RAAS) blockade, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers, has largely been avoided in RTR, because two meta-analyses of otherwise inconclusive data pointed toward an advantage of calcium channel blockers over RAAS blockers for the management of hypertension in this population.[21,22] Moreover, intrinsic effects of RAAS blockade on glomerular filtration rate may mimic rejection. Therefore, many transplant physicians are still reluctant to prescribe them. However, RAAS blockers have been shown to significantly reduce proteinuria in RTR and evidence suggests an advantage of prolonged treatment with this type of drugs in RTR.[23-25]

Alternatives to pharmacological treatment of hypertension

Despite extensive pharmacological treatment, blood pressure management in RTR often remains inadequate. This is illustrated by a recent study using data of the Netherlands Organ Transplant Registry, which showed that in the Netherlands only 23% of RTR meet blood pressure recommendations (Figure 4).[18] Similarly, in a large international cohort (29,751 patients) of the Collaborative Transplant Study, up to 55% of RTR did not reach the goal for blood pressure control.[26] Each 10-mmHg incremental rise in systolic blood pressure independently increases the risk for death and death-censored allograft failure in RTR by 18% and 17%, respectively.[27] Therefore, next to intensifying pharmacological treatment, it is important to identify other modifiable risk factors which allow for intervention. Corticosteroids and calcineurin inhibitors form the cornerstone of post-transplant immunosuppression, but they are widely known to cause hypertension. Therefore, it is important to optimize their dosing regimens to accomplish optimal immunosuppressive effects on the one hand, with as little as possible adverse effects on the other. To be able to do so, gaining knowledge on the dose-response curves and acquiring tools for dose titration are of great importance. Treatment

with calcineurin inhibitors is already closely monitored and doses are continuously adapted to frequently measured blood levels of these drugs. However, treatment with corticosteroids is entirely different. In the Netherlands, the current treatment regimen for corticosteroids encompasses a 'one-size-fits-all' approach with an empirical dose of usually 7.5 mg prednisolone per day, irrespective of body size and/or steroid sensitivity. The main reason for this approach is that there is currently no way to guide intensity of treatment.[17] Thus, personalization of corticosteroid treatment could be an interesting strategy to reduce blood pressure (as well as other adverse effects of corticosteroids, such as glucose intolerance, osteoporosis and sarcopenia), as will be outlined in the paragraphs below. Nevertheless, since treatment with either calcineurin inhibitors and/or corticosteroids will likely remain necessary in the majority of RTR in the near future, alternative strategies to reduce blood pressure also have to be considered. Lifestyle interventions, such as weight reduction, increasing physical activity, cessation of smoking, and reduction of sodium intake, have shown to be effective in reducing blood pressure in other populations and have great potential to reduce blood pressure in RTR. However, they have only been sparsely studied in this population.

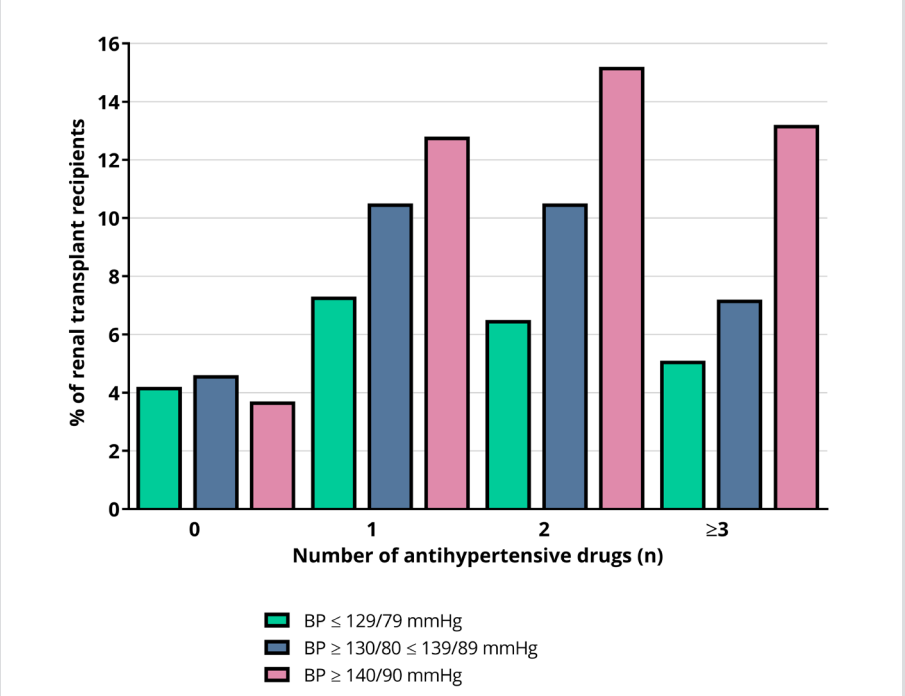

Figure 4. Blood pressure (BP) targets and the use of antihypertensive drugs in renal transplant recipients in the Netherlands. Reprinted with permission from Dobrowolski *et al*.[16]

Sodium restriction as therapeutic strategy

Dietary sodium restriction effectively reduces blood pressure and proteinuria in patients with chronic kidney disease (CKD).[28-31] Moreover, several studies have shown that low sodium intake is associated with much better kidney disease and cardiovascular outcomes in patients with CKD.[32] Therefore, the KDOQI and DASH guidelines advocate a maximum sodium intake of 100 mmol per day for all patients with kidney disease. Despite these recommendations, average sodium intake in RTR largely exceeds this recommendation, with intakes of 150 to 200 mmol per day.[18,33-36] Moreover, treatment with calcineurin inhibitors and corticosteroids, in addition to decreased kidney function and prevalent obesity, may render blood pressure even more sodium sensitive in RTR compared with patients with CKD. This is illustrated by a recent study in 660 Dutch RTR, showing an independent association of sodium intake with blood pressure.[33] In addition, recent studies showed that treatment with the calcineurin inhibitor tacrolimus increases renal tubular sodium absorption.[37] Thus, although evidence points towards potential benefits of dietary sodium restriction in RTR, no randomized clinical trials studying dietary sodium restriction in RTR are available to date.

Sodium status and aldosterone

High sodium intake is even more deleterious when it is accompanied by high serum aldosterone. Aldosterone is one of the main effector hormones of the RAAS, and its main function is to restore volume status in times of sodium and/or volume depletion. It does so by activating the mineralocorticoid receptor, leading to increased renal tubular sodium and water reabsorption and potassium excretion. Therefore, increased aldosterone production leads to hypertension and volume overload. In addition, aldosterone is known to exert pro-fibrotic and pro-inflammatory effects on the vasculature. Interestingly, detrimental effects of aldosterone are only observed in states of primary increase in aldosterone concentrations, rather than states in which increased aldosterone concentrations are secondary to volume depletion. For example, in patients with resistant hypertension the effects of high sodium intake on proteinuria are most pronounced in patients with the highest aldosterone.[38] In contrast, in case of hyperaldosteronism secondary to volume depletion, such as routine low-sodium intake in Yanomami Indians or Gitelman or Bartter syndrome with renal sodium loss, hypertension and cardiovascular damage are absent.[39,40] Taken together, these data suggest that aldosterone mostly exerts adverse effects when its serum concentration is inappropriately high for the prevailing sodium status.

Corticosteroids – Two sides of the medal

Another important contributor to hypertension and cardiovascular disease in RTR is treatment with corticosteroids. Corticosteroids were among the first drugs used to

prevent and treat rejection after kidney transplantation, and are still used to date.[41,42] The most often used corticosteroids after transplantation are prednisone and its bioactive metabolite prednisolone, and in the University Medical Center Groningen (UMCG) prednisolone is exclusively used. Prednisolone exerts its immunosuppressive effects by binding to the glucocorticoid receptor (GR), of which cortisol is the natural ligand. It also binds to the mineralocorticoid receptor (MR), of which aldosterone is the natural ligand. Through its ability to bind both GR and MR, prednisolone causes a wide range of side effects, including weight gain, lipid derangement, glucose intolerance, and hypertension[41,42], thereby adding to the increased cardiovascular risk after kidney transplantation. Therefore, there has been a great effort to get rid of corticosteroids as part of maintenance immunosuppressive regimens after kidney transplantation.[8,42] Nevertheless, it has recently been concluded that corticosteroids have to remain part of the immunosuppressive regimen in order to maintain low acute rejection rates and optimal long-term allograft survival.[43,44] As mentioned earlier, corticosteroid dosing regimens unfortunately remain empiric to date, usually with fixed doses independent of either body size and/or steroid sensitivity.[17] Therefore, tools are needed to monitor and personalize corticosteroid therapy in order to reduce corticosteroid-related adverse effects.

Cortisol synthesis and metabolism

Corticosteroids are synthetic derivatives of endogenous cortisol. Because of their strong structural similarity to endogenous cortisol, they are able to bind the GR and interfere in cortisol synthesis and metabolism (Figure 5 and 6). Under physiological conditions, cortisol synthesis is regulated by the hypothalamus-pituitary-adrenal (HPA) axis. When this axis is activated, the hypothalamus secretes corticotropin releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) by the pituitary, which then stimulates cortisol synthesis by the adrenal glands. Cortisol, in turn, exerts inhibitory effects on the hypothalamus and pituitary via a negative feedback mechanism, thereby regulating its own production (Figure 6). Cortisol is metabolized to biologically inactive cortisone by the enzyme 11beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2), whereas its counterpart 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates cortisol back from cortisone (Figure 5 and 6).[45,46] Both cortisol and cortisone are acted upon by 5α- and 5β-reductases and 3α-hydroxysteroid dehydrogenase, ultimately leading to generation of tetrahydrocortisol (THF), allo-tetrahydrocortisol (allo-THF), and tetrahydrocortisone (THE) (Figure 6). Especially 11β-HSD enzymes play a pivotal role in systemic cortisol availability, with 11β-HSD1 in the liver generating about 30-40% of daily cortisol production, and 11β-HSD2 in the kidney inactivating a similar portion.[45]

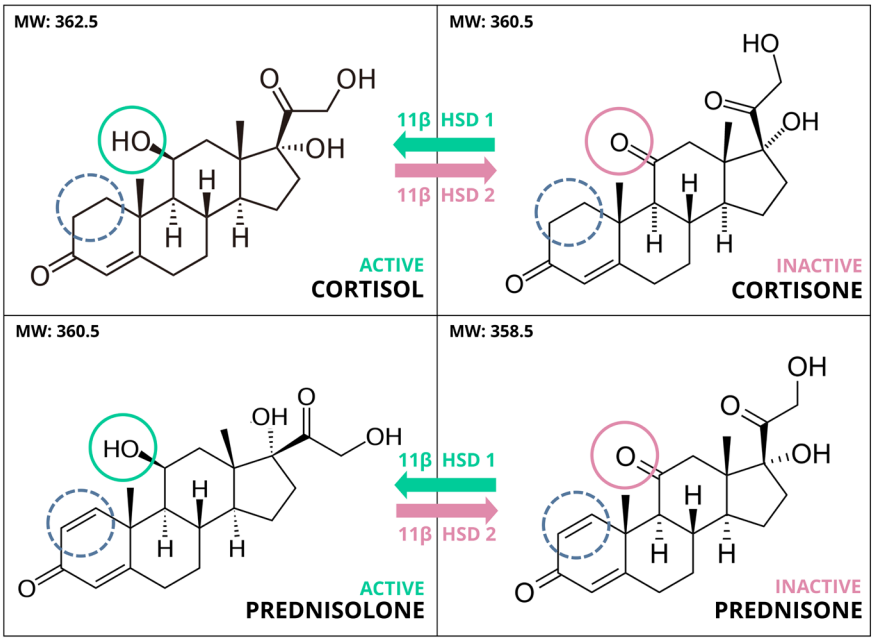

Figure 5. Structural similarities and differences between endogenous cortisol and cortisone, and exogenous prednisolone and prednisone. Green and pink circles indicate differences between activated (green) and inactivated (pink) corticosteroids; dashed blue circles indicate differences between endogenous cortisol and cortisone, and exogenous prednisolone and prednisone. Abbreviations: 11β-HSD1, 11beta-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11beta-hydroxysteroid dehydrogenase type 2; MW, molecular weight.

Corticosteroids and cortisol metabolism

Chronic prednisolone treatment after kidney transplantation is known to suppress the HPA axis, leading to reduced endogenous cortisol synthesis by the adrenal gland (Figure 6).[47-49] Moreover, recent studies in other populations suggest that exogenous corticosteroids could also interfere in cortisol metabolism by altering 11β-HSD enzyme activity (Figure 6).[50-52] To date, the majority of RTR in the UMCG are still treated with prednisolone. Therefore, it would be interesting to investigate whether HPA axis activity and 11β-HSD enzyme activities are altered in these prednisolone-treated RTR compared to subjects of the general population. In addition, it would be even more interesting to investigate whether the degree to which prednisolone alters cortisol production and metabolism is related to the degree of prednisolone exposure in these patients, and thus with metabolic side effects and risk of (cardiovascular) mortality long-term after kidney transplantation.

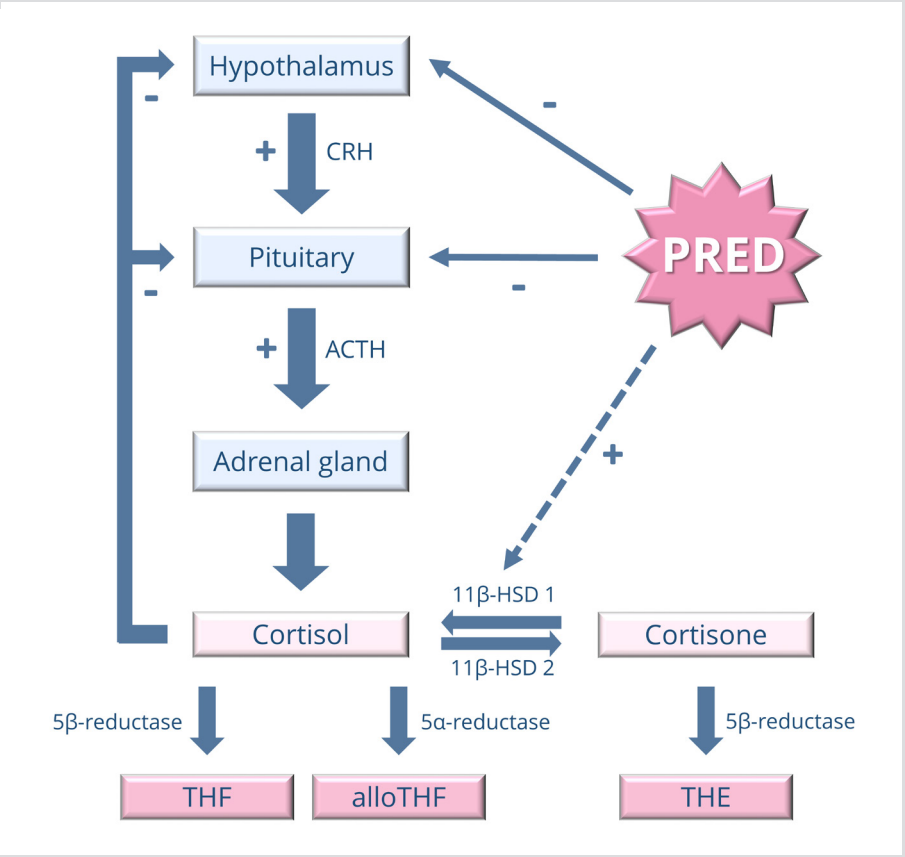

Figure 6. Cortisol synthesis and metabolism, and supposed effects of prednisolone. Abbreviations: CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone; 11β-HSD1, 11beta-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11beta-hydroxysteroid dehydrogenase type 2; THF, tetrahydrocortisol; alloTHF, allo-tetrahydrocortisol; THE, tetrahydrocortisone; PRED, prednisolone.

Systemic inflammation – A new player in the field

A major effect of corticosteroids is to suppress inflammation, not only locally in transplanted organs, but also systemically, in the organism hosting the transplanted organ. Interestingly, systemic inflammation is increasingly acknowledged as a risk factor for cardiovascular morbidity and mortality in the general population.[53-55] In RTR, systemic inflammation is also known to influence outcome. For example, high sensitivity C-reactive protein (CRP) has been found to be independently associated with major cardiovascular events and all-cause mortality in RTR.[56,57] In addition, it was found to be associated with long-term allograft failure after kidney transplantation.[58,59]

The tryptophan-kynurenine pathway

An interesting pathway that is tightly linked to systemic inflammation and corticosteroid exposure is the kynurenine pathway. In contrast to CRP, which is a more constitutional marker of inflammation, the kynurenine pathway may be more open to modification, because it is the major metabolic pathway of the essential amino-acid tryptophan. Under physiological conditions, tryptophan is metabolized to kynurenine by tryptophan 2,3-dioxygenase (TDO) in the liver. However, under inflammatory conditions, extra-hepatic indoleamine 2,3-dioxygenase (IDO) is activated and additionally metabolizes tryptophan to kynurenine.[60,61] In the next step of the pathway, kynurenine is metabolized to cytotoxic 3-hydroxykynurenine by kynurenine 3-monooxygenase (KMO) (Figure 7).[61] Both IDO and KMO enzymes are activated by pro-inflammatory stimuli and are expressed in a variety of tissues and immune cells.[62] Interestingly, in experimental animal studies, IDO activation by pro-inflammatory stimuli is enhanced by GR and MR activation by exogenous dexamethasone, corticosterone and aldosterone, suggesting that corticosteroids interact with inflammatory stimuli to enhance kynurenine synthesis.[63]

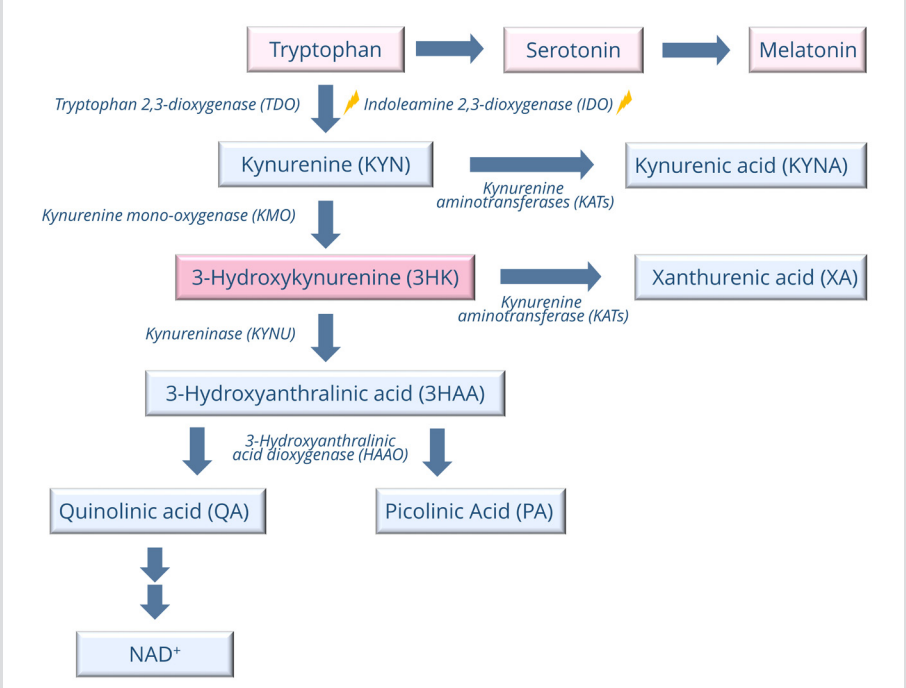

Figure 7. The tryptophan-kynurenine pathway. High-lighted in dark pink is the toxic kynurenine metabolite 3-hydroxykynurenine.

Modification of the kynurenine pathway as therapeutic strategy

Kynurenine and particularly down-stream cytotoxic 3-hydroxykynurenine are thought to play an important role in systemic inflammation. As such, accumulation of kynurenine metabolites has been linked to the development of atherosclerosis and cardiovascular disease,[64-69] particularly in patients with kidney disease.[70-72] Because the kynurenine pathway is thought to play a role in the pathophysiology of many inflammation-related diseases, there is currently great interest in ways to modify this pathway. Initially, inhibition of IDO gained most interest, because this enzyme catalyzes the first and rate-limiting step of the pathway.[73,74] However, recently inhibition of KMO gained more interest, because this would more directly block production of cytotoxic 3-hydroxykynurenine.[73-76] In RTR, activation of the kynurenine pathway has been associated with increased risk of acute rejection.[77,78] Thus, modification of the kynurenine pathway seems a promising strategy to reduce systemic inflammation and subsequent risk of cardiovascular disease in other populations, and might too in RTR. However, not much is known of the role of the kynurenine pathway in systemic inflammation in stable RTR and how this affects long-term survival of both patient and allograft.

OUTLINE AND AIMS OF THIS THESIS

Cardiovascular risk is greatly increased in RTR, which is due to an interaction of traditional and transplantation-related cardiovascular risk factors, and impairs long-term patient and allograft survival after transplantation. In addition, in the setting of kidney transplantation, several traditional cardiovascular risk factors are more prevalent, more severe, or less responsive to treatment than in non-transplanted patients. However, few adequate specific guidelines for cardiovascular risk management in RTR exist, and current guidelines are mainly based on strategies for other (high risk) populations. Therefore, the overall aim of this thesis is to make the first steps towards personalized cardiovascular risk management in RTR. More specifically, this thesis aims to identify modifiable risk factors that allow for intervention and development of RTR-specific treatment strategies, which ideally address both traditional and transplantation-related cardiovascular risk factors. In addition, it aims to identify biomarkers that allow for personalization of treatment of the individual transplant recipient.

Hypertension is the most prevalent of all cardiovascular risk factors in RTR, and sodium intake is known to be an important contributing factor. In **Chapter 2** we investigate the effects of dietary sodium restriction on blood pressure and albuminuria in stable RTR. Using a randomized cross-over design, we compare a sodium restricted diet with a normal sodium diet. High sodium intake is especially deleterious when serum aldosterone concentrations are also high. In **Chapter 3** we review the effects of aldosterone on the kidney and vasculature, and the interaction of sodium status with aldosterone. In addition, we review potential therapeutic strategies to reduce the combined effects of these evil twins.

Prednisolone treatment after kidney transplantation is associated with numerous metabolic side effects, including hypertension, which contribute to increased cardiovascular risk in RTR. It is also known to suppress endogenous cortisol production, by suppressing the hypothalamus-pituitary-adrenal (HPA) axis. In addition, prednisolone treatment has been suggested to alter systemic cortisol exposure by interfering in the enzymes that (in)activate cortisol, the 11-beta hydroxysteroid dehydrogenases (11β-HSDs).

In **Chapter 4** we investigate whether HPA axis activity, as measured by 24h urinary cortisol excretion, is altered in prednisolone-treated RTR, and whether the degree of HPA axis suppression is related to metabolic side effects of prednisolone. In **Chapter 5** we go one step further, and zoom in not only on the effects of prednisolone on the HPA axis, but also on 11β-HSD activity, and compare RTR to healthy controls. By using

the 24h urinary cortisol metabolite profile to assess these parameters, we investigate whether altered HPA axis and 11β-HSD activity is associated with long-term (cardiovascular) mortality in prednisolone-treated RTR.

Finally, we shed our light on the effects of systemic inflammation on long-term outcome after kidney transplantation. To this end, we study activation of the pro-inflammatory tryptophan-kynurenine pathway, and its association with long-term outcome after kidney transplantation in **Chapter 6**.

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